REMARKS

Claim Amendments

Claims 29 and 30 have been cancelled and claims 21-24, 27-28 31-34 have been amended as follows:

- Independent claims 27 and 28 have been amended to remove the recitation of "excluding AZD2171 maleate salt." Support for these claims as amended is found in the specification, *inter alia*, at page 5, lines 21-25 (claim 27) and at page 11, lines 21-26.
- Claim 21 has been amended to be dependent on claim 27 or claim 28 only, and the dependency has been reworded in a manner to be consistent throughout the claims. Support for this claim as amended is found in the specification, *inter alia*, at page 18, lines 30-31.
- Claims 22-24 have been amended to reword their dependency in a manner to be consistent throughout the claims. Support for these claims as amended is found in the specification, *inter alia*, at page 4, lines 16-18.
- Claims 31-33 have been amended to be dependent on claim 27 or claim 28. Support for these claims as amended is found in the specification, *inter alia*, at page 16, lines 13-29.

The above amendments are being made to encompass all salt forms in the same claim set and to adjust the dependencies accordingly, without deleting any subject matter from the scope of the claims as a whole. It should be clear from the above that no new matter has been added by the above amendments, and entry thereof is believed to be in order and is respectfully requested. Following entry of the above amendment claims 21-24 and 27-28 and 31-34 are pending in this application.

Priority

Under the heading "priority" the Examiner states that the "earliest effective US filing date afforded the instantly claimed invention is 03/22/2005, the filing date of PCT/GB05/01079." While this is correct, the actual "*priority*" that has been claimed, and to which the presently claimed invention is entitled, is to GB application 0406450.7 filed March

23, 2004 and GB application 0407755.8 filed April 6, 2004. It is noted that the Examiner has acknowledged the priority claim in paragraph 12 of the Office Action Summary, and has checked box "a) All", but has not checked one of boxes 1, 2 or 3. It is presumed that certified copies of the priority documents have been received in this National Stage application from the International Bureau, and completion of this acknowledgement would be appreciated.

Claim Objection

The objection to claim 29 has been obviated by the cancellation of this claim by the above amendments.

Double Patenting

Claims 21-24 and 27-34 are *provisionally* rejected on the ground of nonstatutory obviousness-type double patenting "as being unpatentable over claims 1-6 of copending Application No. 10/563439; 10563,440; 10/594,233; 10/594,234; 11,663,912 in view of Lee (US Pub No. 2002/0002162; Pub.Date Jan.3,2002)." (Action at page 3). The Examiner's attention is called to the fact that Application No. 10/563,440 is listed as "abandoned" in PAIR, with no pending continuing application. Otherwise, these applications all remain pending with no claim allowed. Therefore this obviousness-type double patenting rejection remains provisional.

While Applicant does not agree with the Examiner's argument of obviousness-type double patenting, in particular with respect to the application of the Lee reference to this rejection (for reasons discussed below), Applicant need not, and in fact cannot respond to this ground for rejection unless and until claims are allowed in the reference applications before allowance of the present application.

Claim Rejections - 35 USC § 103

Claims 21-24 and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee, US Pub No. 2002/0002162 (hereinafter "**Lee '162**") in view of Hilberg *et al.* WO/2004/096224 (hereinafter "**Hilberg '224**). This ground for rejection is respectfully traversed.

First, the Examiner has made a note after the citation of Hilberg '224 that reads "Prior.date 02/29/2003", and the undersigned is unable to figure out what this note is

intended to refer to. The earliest of the three different "priority dates" claimed in Hilberg '224 is April 29, 2003 (not February), and this clearly is not the date on which this reference is *effective as prior art* in the United States. In fact, the *earliest* date on which Hilberg '224 is *effective as prior art* in the United States is its International Filing Date of April 24, 2004. There is no way that this document can be considered *effective as prior art* as of any of its European priority dates.

As noted above under ***Priority***, the present application has claimed and is entitled to priority as of the filing dates of its priority applications GB application 0406450.7 filed March 23, 2004, and/or GB application 0407755.8 filed April 6, 2004, both of which were filed before the earliest *effective prior art date* of Hilberg '224 of April 24, 2004.

It seems that perhaps the Examiner is confusing *priority dates* with *prior art effective dates*. Simply put, a reference document is prior art to an application if the reference is *effective as prior art* on a date that is earlier than the *priority date* to which the application is entitled. Thus again, because Hilberg '224 has an *earliest effective prior art* date of April 24, 2004, which is after both *prior art* dates accorded the present application, Hilberg '224 is not prior art to the present application.

Therefore, this ground for rejection based on Lee '162 in view of Hilberg '224 must be withdrawn.

Moreover, it is respectfully submitted that the Examiner has mischaracterized what Lee '162 "teach" when asserting in the Action:

> Lee '162 , teaches therapies for treatment of cancer , that further, teach a synergistic method for the treatment of cancer in a mammalian specie[0002,0011] which comprises a vascular endothelial growth factor receptor tyrosine kinase inhibitor, ZD6474 [0082], in conjunction with carboplatin [0079], cisplatin and oxaliplatin [Table 1] for the treatment of breast, pancreas, bladder colon lung, skin colorectal, non-small cell lung cancer and mesothelioma.[0059-0067].

(Action at page 3; emphasis added).

The actual "teaching" of Lee '162, under any reasonable construction of this reference, and as specifically stated in paragraph [0011], which the Examiner is purportedly paraphrasing:

> The present invention provides a synergistic method for the treatment of cancer which comprises administering to a mammalian specie in need thereof a synergistically, therapeutically effective amount of: (1) at least one agent selected from the group consisting of anti-proliferative cytotoxic agents and anti-proliferative cytostatic agents, and (2) a compound of formula I ...

(Lee '162 [0011]); emphasis added. In particular:

- Lee '162 does not *teach*, no less even suggest, synergism with any combination *except with Bristol-Myers' proprietary formula I;*[1]
- Lee '162 does not *teach*, no less suggest, "a vascular endothelial growth factor receptor tyrosine kinase inhibitor, ZD6474 [0082], in conjunction with carboplatin [0079], cisplatin and oxaliplatin [Table 1]" as the Examiner states; and
- Lee '162 certainly does not *teach*, no less suggest, that "synergism" might be obtained by administering a VEGF RTK inhibitor "in conjunction with carboplatin, cisplatin and oxaliplatin" as the Examiner seems to be suggesting.

Thus, the emphasis throughout Lee '162 is on, first and foremost, the administration of a compound of formula I *in every instance*, in combination with at least one agent selected from the group consisting of antiproliferative cytotoxic agents and antiproliferative cytostatic agents.

It is understood that the Examiner is trying to make a case for other combinations because of the "at least one" recitation, but in every instance there is the mandatory presence of the compound of formula I, and it is *only* with the combinations *with formula I* that any synergistic effect is suggested. There is no suggestion anywhere in this reference that *any* benefit (synergistic or not) might be achieved by combining any one of the "antiproliferative cytotoxic agents and antiproliferative cytostatic agents" with any other such agent, except in the presence of a compound of formula I.

Moreover, there is no named or exemplified two-component composition in this reference that includes ZD6474 with the compound of formula I; and there is no three or

[1] Paragraph [0007] of Lee '162 states that US Patent 6,011,029 discloses the formula I compounds. Both Lee '162 and US Patent 6,011,029 state the assignee as Bristol-Myers Squibb.

more component composition that includes ZD6474 or any VEGF RTK inhibitor together with a platinum compound (necessarily also including a compound of formula I).

Instead, ZD6474 and platinum compounds are simply and separately included within the massive list of "anti-proliferative cytotoxic agents and anti-proliferative cytostatic agents" extending over paragraphs [0071] through [0083] from which at least one of such agents is selected for combination with the compound of formula 1. Even under the less rigorous criteria for evaluating obviousness set out by the Supreme Court in *KSR v. Teleflex*, 127 S. Ct. 1727, 82 USPQ2d 1385, there still must be at least some good reason for the skilled person to make the particular selections and the combination thereof to achieve Applicants' invention, without use of hindsight. It is respectfully submitted that there is *no* such reason evidenced by this (or any other reference cited by the Examiner). Moreover, it is respectfully submitted that no reasonable, skilled person would waste his or her time consulting an omnibus listing of most every known anti-cancer agent such as this, when looking for effective combination cancer therapies. Therefore, whether or not Hilberg '224 is considered to be prior art to the presently claimed invention (which it is not), *prima facie* obviousness has not been shown, and this ground for rejection should be withdrawn.

Previous claims 29-34 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lee '162 in light of Hilberg '224, and "further in view of Lane et al (US Pub.No. 204/0147541; PCT filed (02/18/2002)" (hereinafter "Lane '541"). The above refutations of the rejections based on Lee' 162 and Hilberg '224 apply here as well. Lane '541 is applied here only with respect to the "salt" aspect of previous claims 29 and 30, which recited the maleate salt of AZD2171, and claims 31-34, which were dependent on claims 29 and 30. Claim 29 and 30 have been cancelled by the above amendments, and the dependency of claims 31-34 has been amended to be dependent on claims 27 and 28. Therefore, this ground for rejection has been obviated.

Information Disclosure Statement

For completeness of the record, a supplemental Information Disclosure Statement and form PTO-1449 is being submitted herewith on which is listed WO2005/061488, which is the publication of International Patent Application No. PCT/GB2004/005359 that is cited on

page 3 of the present specification. However, it should be noted that WO2005/061488 is *not* prior art to the present application, in that its earliest *prior art effective date* is the December 18, 2004 filing date of PCT/GB2004/005359. This is subsequent to *priority date* to which the presently claimed invention is entitled, *i.e.,* the *latest* of the two priority applications to which priority is claimed for the present application is GB application 0407755.8 filed April 6, 2004. This PCT application entered the US National Stage on June 1, 2006 as US application 10/581,279, which published as US 20070129387A1 on June 7, 2007, and is currently pending with Examiner Tamthom Ngo Truong in GAU 1624, with a predicted first Action in 4 months from the present date.

Technically Related Pending Applications of Applicant's Assignee

The Examiner's attention is called to the following *updated* Table of pending U.S. applications of Applicants' assignee which might be considered technically related, each of which claims a combination of AZD2171 with another therapeutic agent identified under the heading "Combination." The current status of each application as reported in the PAIR database is given in the right-hand column. Each of the published US applications and PCT applications that are in bold on the below table are listed on the form PTO-1449 attached to the Information Disclosure Statement being submitted herewith, and a copy of each such bold listed published PCT application is provided with the Information Disclosure Statement. All other documents have been previously listed and copies provided in this application.

It is assumed that the Examiner has ready electronic access to each of the pending US applications, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

US Appln. No.	**Date US Filed**	**US Pub. No. Date Published**	**PCT Pub. No. Date Published**	**Combination with**	**Current Status**
10/240,413	October 1, 2002	US 20030144298 July 31, 2003	WO 01/74360 October 11, 2001	Anti-hypertensive	Assigned to Examiner Charlesworth E Rae in GAU 1611; Final Rejection Mailed 10-02-2008.

US Appln. No.	Date US Filed	US Pub. No. Date Published	PCT Pub. No. Date Published	Combination with	Current Status
10/555,389	November 3, 2005	**US 20060223815** October 5, 2006	**WO 2004/098604** November 18, 2004	Anti-angiogenic agent + src inhibitor	Assigned to Examiner Christopher R. Stone in GAU 1614; Response to Non-Final Office Action Entered and Forwarded to Examiner.
10/563,440	January 5, 2006	US 20060160775 July 20, 2006	WO 2005/004871 January 20, 2005	ZD6126	Abandoned
10/563,439	January 5, 2006	US 20060167024 July 27, 2006	WO 2005/004872 January 20, 2005	ZD1839	Assigned to Examiner Benjamin J Packard in GAU 1612; Non Final Action Mailed 09-10-2008.
10/594,235	September 25, 2006	US 20080113039 July 17, 2008	WO 2005/092384 October 6, 2005	Platinum anti-tumor agent, optionally IR	Assigned to Examiner Sharmila Gollamudi Landau in GAU 1611; Non Final Action Mailed 10-03-2008.
10/594,233	September 25, 2006	US 20080125447 August 11, 2008	WO 2005/092303 October 6, 2005	CPT-11 and/or 5-FU	Assigned to Examiner Sharmila Gollamudi Landau in GAU 1611; Non-Final Action Mailed 10-29-2008.
10/594,234	September 25, 2006	US 20070135462 June 14, 2007	WO 2005/092385 October 6, 2005	Taxane. optionally IR	Assigned to Examiner Charlesworth E Rae in GAU 1611; Response to Non-Final Office Action Entered and Forwarded to Examiner.
11/663,912	March 27, 2007	US 20080015205 January 17, 2008	WO 2006/035203 April 6, 2006	Imatinib [Gleevec]	Assigned to Examiner James D. Anderson in GAU 1614; Non Final Action Mailed 09-22-2008.
11/994,824	January 4, 2008		WO 2007/003933 January 11, 2007	Gemcitabane [Gemzar]	Assigned to GAU 1636, no Examiner assigned; predicted first Action 17 months.
12/158,266	June 19, 2008	**US 20080306094** December 11, 2008	WO 2007/071970 June 28, 2007	pemetrexed	Assigned to Anna Pagonakis in GAU 1614; Non Final Action Mailed 03-25-2009.
12/097,384	June 13, 2008		**WO 2007/068895** June 21, 2007	Angiopoietin-2 antagonist and antagonist of VEGF-A, and/or KDR, and/or Flt1	Assigned to GAU 1644, no Examiner assigned.

The Examiner's Attention is also called to the following Table of a pending U.S. application of Applicants' assignee which may be considered technically related, which claims a combination of a platinum anti-tumour agent with another therapeutic agent identified under the heading "Combination." The current status of this application as reported in the PAIR database is given in the right-hand column. The published US applications and PCT application were previously cited in this application and a copy of the published PCT application was previously provided.

Again, it is assumed that the Examiner has ready electronic access to this pending US application, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

US Appln. No.	Date US Filed	US Pub. No. Date Published	PCT Pub. No. Date Published	Combination with	Current Status
10/536,668	August 27, 2005	US 20060167027 July 27, 2006	WO 2005/004870 January 20, 2005	ZD6474	Pending before Examiner Madhu Khanna in GAU 2451; Non Final Action Mailed 12-23-2008.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
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